Original Article

Association Between Maternal Hyperuricemia and Small for Gestational Age Fetuses in Normotensive Pregnant Women

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Abstract

Objective: To investigate the relationship between maternal hyperuricemia and the occurrence of small for gestational age (SGA) fetuses in normotensive pregnant women.

Materials and Methods: This case-control study was conducted across two campuses of the Ziauddin University Hospital Karachi, specifically within the Gynecology and Obstetrics Departments, spanning from November 2016 to April 2017. A total of 50 pregnant women with SGA fetuses served as cases, while 50 pregnant women with appropriate for gestational age (AGA) fetuses acted as controls. Inclusion criteria encompassed women aged 20 to 35 years with singleton pregnancies. Serum uric acid levels were assessed in both the case and control groups using blood samples obtained from Ziauddin Laboratory. Data collection was executed using a predefined proforma.

Results: One hundred normotensive women with singleton pregnancies were recruited during the third trimester. The mean maternal age was 27.3 ± 3.5 years in the AGA group and 24.6 ± 3.8 years in the SGA group. The prevalence of hyperuricemia was found to be 17 (34%) in the SGA group compared to 8 (16%) in the AGA group. Maternal elevated uric acid levels during pregnancy were significantly associated with SGA (odds ratio [OR] 2.7, 95% confidence interval [CI] 1.04 – 7.04; p = 0.038). Maternal hyperuricemia was not statistically significant based on BMI (p > 0.05) but showed statistical significance in relation to parity >2 (p = 0.001).

Conclusion: Elevated maternal uric acid levels during pregnancy were notably more prevalent in women with small gestational age fetuses.

Keywords: Uric Acid, Hyperuricemia, Small for Gestational Age, Normotensive.

Cite this article as: Khalid M, Rana MY, Soomro S, Siddique A, Farooq N, Rasul N. Association between Maternal Hyperuricemia and Small for Gestational Age Fetuses in Normotensive Pregnant Wome.. J Soc Obstet Gynaecol Pak. 2023; 13(3):212-216.

Introduction

Uric acid is the end product of the degradation of purine, its metabolization occurred in the liver, is generated from both the exogenous and endogenous precursor proteins.[1] The kidneys and intestines are the major organs responsible for its excretion (65% and 35%, respectively).[1] At physiologic values, uric acid has strong antioxidant activities, accounting for two-thirds of antioxidant capacity of the total plasma. Although the uric acid may cause oxidative damage when it rises over the normal amount in the plasma.[1] In vascular smooth muscle cells, uric acid enhances thromboxane formation, decreases the production of nitric oxide, and boosts the creation of inflammatory and the vasoconstrictors and agents.[2,3] Thus, increased serum uric acid levels are strongly linked to dysfunction of endothelial cells and high blood pressure typically occurs before hyperuricemia.[2] In the everyday clinical practice, the hyperuricemia is a frequent problem that affects between 8.9-24.4% of the population generally.[4] Regardless of the raise in glomerular filtration rate (GFR), higher uric acid level is

Authorship Contribution: [1]Conception & Study Design, Data Collection & Processing, Data Analysis and/or Interpretation.[2,3]Data Analysis and/or Interpretation, [4]Drafting of Manuscript, [5]Active Participation in Active Methodology, [6]Critical Review.

Funding Source: none
Conflict of Interest: none

Received: Mar 26, 2023
Accepted: Aug 19, 2023

still a common issue in pregnancy. It's linked to the with several adverse outcomes of pregnancy.[1]

Premature birth, intrauterine growth restriction (IUGR) lower Apgar score, and perinatal mortality all became more likely with a raised level of uric acid ≥ 393 mol/L.[5] There is a number of hypothesized causes for the rise in serum uric acid, including acidosis, increasing tissue breakdown, aberrant renal clearance, and hypertrophy. Increased serum uric acid concentrations produce inflammation, endothelial dysfunction and oxidative stress which lead to placental malfunction and may have an effect the vascular health of the mothers, increasing the risk of preterm birth.[6,7] SGA has been one of the leading reasons of perinatal mortality. It's not only endangering the development and growth of the newborn in the uterus but also influences young children's and adolescents' mental and physical development as well as resulting in cognitive and behavioral abnormalities, language problems, learning problems, and even an increase in autism incidence.[8-10] Small gestational age newborns may develop as a consequence of the proliferative and inflammatory effects of increasing uric acid on the placenta's small blood capillaries.[11] According to previously published study regarding association between uric acid levels in normotensive pregnant women with insulin resistance and birth weight. SGA occurred in 30.8% of pregnancies in normotensive women with uric acid in the highest quartile (uric acid > 4.1mg/dl) compared to only 3.4% of normotensive women with uric acid in the lowest quartile (uric acid < 2.9mg/dl).[12] According to a prospective, multicentric, cohort study on 404 normotensive singleton pregnant women in Tehran. Out of the patients with maternal hyperuricemia 13.5% had SGA delivery compared to 10.6% of non-hyperuricemia patients. Maternal hyperuricemia was found to be associated with SGA delivery (p=0.02).[1]

The aim of this study was to identify the association of maternal hyperuricemia and small for gestational age fetuses in normotensive pregnant women to understand more about hyperuricemia as a risk factor for SGA fetuses and to identify it early in the pregnancy by performing routine uric acid levels to reduce the poor outcome.

Methodology

This case control study was conducted in 2 campuses of Ziauddin University Hospital Karachi Gynecology and Obstetrics Department, from November 2016 to April 2017. A total of 50 pregnant women with SGA fetuses as cases and 50 pregnant women with AGA fetuses as controls, age 20 – 35 years and singleton pregnancy of either gravidity, were enrolled in the study. All the diagnosed case of essential hypertension, case of Gestational hypertension which includes pregnancy induced hypertension, pre-eclampsia and eclampsia, renal impairment, gestational diabetes mellitus and SGA due to congenital or chromosomal abnormalities were excluded. Written informed consent was taken. The study was conducted after approval of the ethical committee. Prior to enrolment, the purpose, procedure, risks and benefits were explained. Demographics, medical history and physical examination were carried out. Information such as patient's name, age, weight, height, BMI, parity and last menstrual period (LMP) was reported on the proforma. SGA fetus in an enrolled case was determined by the abdominal circumference of the fetus on ultrasound scan. It was defined as birth weight < 10th percentile for gestational age according to gestational age specific predicted values of abdominal circumference. The serum uric acid levels for cases and controls tested on blood samples from Ziauddin Laboratory and recorded. Serum uric acid levels were defined as serum uric acid level one standard deviation greater than the appropriate for gestational age. All data was collected on a pre-designed proforma.

Data was analyzed by using IBM SPSS. 26. Relevant descriptive statistics mean and standard deviation was calculated for quantitative variables like age of patient, height, weight and BMI. Percentages and frequencies were calculated for qualitative variables like SGA of fetus, hyperuricemia and parity. Chi square test was applied whether there is association between SGA and hyperuricemia by taking p = < 0.05 as significant. Confounders like age of patient, BMI and parity were dealt through stratification and post stratification Chi square test was applied by taking p-value < 0.05 as significant and odds ratios were also calculated.

Results

A total of 100 normotensive women with singleton pregnancy were recruited at the third trimester. The mean parity, body mass index (BMI), Weight and height were statistically similar between SGA and AGA group. While mean maternal age was significantly high in AGA group 27.3±3.5) years as compared with SGA group 24.6±3.8) years. P<0.0001. Distribution of parity between two groups is presented in table I, with

insignificant association between SGA and AGA groups (p = 0.15).

Prevalence of hyperuricemia was found 17 (34%) in SGA group versus 8 (16%) in AGA group. Maternal raised uric acid level in the women during pregnancy was significantly associated with SGA (OR 2.7,95% CI 1.04 – 7.04; p-value = 0.038) Table **II**.

Table I: Patient's Demographic Characteristics (n= 100)

	Small for Gestational Age (n = 50)	Appropriate Gestational Age (n = 50)	P-values
Age	24.6 ±3.8	27.3 ±3.5	< 0.0001
Weight	53.2 ±12.4	57.1 ±8.4	0.07
Height	153.5 ±12.1	157.7 ±11.3	0.073
Pre-Pregnancy BMI	22.6 ±4.7	23.3 ±5.4	0.5
Parity	0.9 ±1.3	1.2 ±1.2	0.3

Table II: Association of Maternal Hyperuricemia with Small for Gestational Age and Group (n= 100)

Hyperuricemia	Small for Gestational Age (n = 50)	Appropriate Gestational Age (n = 50)	P-value	OR (95% CI)
Yes	17 (34%)	8 (16%)	0.038	2.7 (1.04 – 7.04)
No	33 (66%)	42 (84%)		

Confounders like age of women, BMI and parity were dealt through stratification. Frequency of hyperuricemia was high in SGA group 12 (38.7%) as compared to AGA group 2 (20%) but the difference was statistically insignificant. (p = 0.28). Frequency of hyperuricemia was significantly high in SGA group 6 (33.3%) as compared to AGA group 2 (8.3%). (p = 0.04). While in overweight women frequency of hyperuricemia was high in AGA group 4 (33.3%) as compare to SGA group 5 (29.4%). but the difference of frequency was statistically insignificant. (OR 0.83, p-value = 0.8). In multiparous women, frequency of hyperuricemia was significantly high in SGA group 5 (62.5%) p-value< 0.001. While no association was seen in nulliparous women and women with parity one Table **III**.

Discussion

Pregnancy-related hyperuricemia is linked to a poor foetal outcome. The placenta's ability to transport amino acids is directly inhibited by uric acid, which also slows foetal growth.[11]

In the smooth muscle cells of the vessels, uric acid enhances thromboxane synthesis, decreases nitric oxide synthesis, and boosts the production of vasoconstrictors and inflammatory mediators.[11,13] This study has been done to assess the relationship between maternal raised uric acid level among and SGA among normotensive women during pregnancy. In this study mean maternal age was significantly high in AGA group 27.3±3.5) years as compared with SGA

Table III: Maternal Hyperuricemia According to Maternal Age, BMI and Parity (n = 100)

Variables	Hyperuricemia	Small for Gestational Age (n = 50)	Appropriate Gestational Age (n = 50)	P-values (OR)
< 25 (Years)	Yes	12 (38.7%)	2 (20%)	0.28 (2.5)
	No	19 (61.3%)	8 (80%)	
≥ 25 (Years)	Yes	5 (26.3%)	6 (15%)	0.3 (2)
	No	14 (73.7%)	34 (85%)	
Under Weight	Yes	3 (25%)	2 (20%)	0.78 (1.33)
	No	9 (75%)	8 (80%)	
Normal	Yes	6 (33.3%)	2 (8.3%)	0.04 (5.5)
	No	12 (66.7%)	22 (91.7%)	
Over Weight	Yes	5 (29.4%)	4 (33.3%)	0.8 (0.83)
	No	12 (70.6%)	8 (66.7%)	
Obese	Yes	3 (100%)	0	NA
	No	0	4 (100%)	
0	Yes	7 (28%)	4 (22.2%)	0.67 (1.4)
	No	18 (72%)	14 (77.8%)	
1	Yes	5 (29.4%)	4 (25%)	0.78 (1.3)
	No	12 (70.6%)	12 (75%)	
≥ 2	Yes	5 (62.5%)	0	< 0.001 (NA)
	No	3 (37.5%)	16 (100%)	

group 24.6 ±3.8 years. While mean parity, body mass index (BMI), Weight and height were statistically similar between SGA and AGA group. In this study overall 25% of the women during pregnancy with normal blood pressure had hyperuricemia that exceeds the anticipated occurrence. This demonstrates that the population that was studied by Lind et al. had lower uric acid concentrations than the group that was studied in this study.[14]

A study from Iran reported similar prevalence 25.4% of hyperuricemia among normotensive pregnant women. These findings were also comparable to the findings of some other studies.[15-17] Nevertheless, several publications indicated lower rates of hyperuricemia. These variations could be associated to the socioeconomic, geographical variations, dietary variations and sample selection criteria.

In this study among normotensive women during pregnancy, raised maternal uric acid level was significantly linked to small gestational age (OR 2.7, 95% CI 1.04 – 7.04; p-value = 0.038). Consistently Amini E etal[1] reported that, in the normotensive women with singleton pregnancy, maternal raised uric acid concentration is significantly linked to premature birth and SGA as well as the onset of neonatal intraventricular hemorrhage. Our findings were also similar with other publications done in various populations and at various stages of pregnancy, as Akahori Y et al[11] reported that the in the normotensive females during pregnancy, the rising maternal uric acid values were linked to small gestational age and mildly reduced kidney function.

On the other hand, Faryal Noman NN et al[18] reported that the prevalence of poor APGAR scores in new borns born to normotensive women with raised uric acid level, differs significantly from those born to normotensive women without hyperuricemia. The consistency of the relationships across publications conducted under various conditions and the response occurring prior to the consequence are two crucial criteria in determining the causal link of factors that are associated, and these findings meet both of them. Confounders like age of women, BMI and parity was dealt through stratification. In younger age (< 25 years) women, prevalence of hyperuricemia was high in SGA group 38.7% as compared to AGA group 20% (OR 2.5, *p-value = 0.28*). Same results were found in women with age ≥ 25 years. In normal weight women, hyperuricemia were significantly high in SGA group 33.3% as compared to AGA group 8.3% (OR 5.5, p-value = *0.04*). While in overweight women frequency of hyperuricemia was high in AGA group 33.3% as compare to SGA group 29.4%. but the difference was statistically insignificant. (OR 0.83, *p-value = 0.8*). In multiparous women hyperuricemia was significantly high in SGA group 62.5% p-value< 0.001. While no association was seen in nulliparous women and women with parity one.

Our findings, in accordance with studies demonstrating the free transfer of uric acid through the placenta,[19] support the idea that the raised uric acid in maternal serum may be the cause of SGA. These findings show a significant correlation between maternal hyperuricemia and the SGA of the newborn. The pro oxidative properties of uric acid and its capacity to foster inflammation and endothelial dysfunction may be the cause of this vicious effect of uric acid.[20]

Conclusion

Maternal raised uric acid level in the women during pregnancy was observed to significantly high among women with small gestational age. It can be assumed as a prognostic factor of small gestational age. However further supportive large-scale studies are recommended.

Limitations: Although the current study has several limitations, specially this was a limited sample size and single centre study, therefore further large-scale studies are recommended to the implementary conclusive findings.

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